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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/693,056	10/24/2003	Joost A. Kolkman	022013-000160US	1550

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EXAMINER	
LIU, SUE XU	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 11/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/693,056	KOLKMAN ET AL.	
	Examiner	Art Unit	
	Sue Liu	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *95-107* is/are pending in the application.

4a) Of the above claim(s) *99,102,104 and 105* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *95-98, 100, 101, 103, 106, 107* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *see the attachments*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

Claims 1-94 have been cancelled filed on 4/17/06;

Claims 95-107 are currently pending;

Claims 99, 102, 104 and 105 have been withdrawn;

Claims 95-98, 100, 101, 103, 106 and 107 are being examined in this application.

Election/Restrictions

1. Applicants elected the following species:

(A) the following number of monomer domains: two

(B) the following specific sequence for the first monomer domain: CPANEFQCRNSSTCIPRRWLCDGDDDCGDGSDETGCSAPASEPPGSL;

(C) the following specific sequence for the second monomer domain: CQPDQFRCSSGRCLSREWLCDGEDDCEDDSDETDCPTRTSLQ;

(F) the following cells: bacterial cells;

(G) the following first target molecule: IgE;

(H) the following second target molecule: IgE;

in the Reply filed on 10/16/06 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Accordingly, Claims 99, 102, 104 and 105 have been withdrawn due to non-elected species.

Priority

2. This application is a CIP of 10/289,660 (filed on 11/06/2002; now ABN), which is a CIP of 10/133,128 (filed 04/26/2002), which claims benefit of the following provisional applications:

60/374,107 04/18/2002;

60/333,359 11/26/2001;

60/337,209 11/19/2001;

60/286,823 04/26/2001.

3. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention, which is also disclosed, in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/286,823, filed on 4/26/01, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The current application obtains the priority date of 60/337,209.

Thus, the effective filing date of the instant application is 11/19/01.

Information Disclosure Statement

4. The information disclosure statement filed 8/16/2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The copies of the cited the foreign patent documents and the non-patent literature publications are not found in the parent case 10/133,128. It has been placed in the application file, but the information referred to therein in regard to the foreign patent documents and the non-patent literature publications has not been considered, as indicated on the attached IDS form.

Oath/Declaration

5. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

For inventor, Per-Ola Freskgard:

It does not identify the city and either state or foreign country of residence of each inventor. The residence information may be provided on either an application data sheet or supplemental oath or declaration.

It does not identify the mailing address of each inventor. A mailing address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The mailing address should include the ZIP Code designation. The

mailing address may be provided in an application data sheet or a supplemental oath or declaration. See 37 CFR 1.63(c) and 37 CFR 1.76.

Objections to the Claims

1. Claim(s) 1 is/are objected to because of the following informalities:

A. Claim 106 repeats the word domain twice (i.e., "***monomer domains domain variants***") in line 2. Correction is requested.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 95-98, 100, 101, 103, 106 and 107 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 95 recites the limitation that the monomer domains (or variant thereof) comprise "non-naturally-occurring amino acids sequences", which the term "non-naturally occurring" is broadly defined in the instant specification. The instant specification discloses that the term "naturally occurring" is used herein to indicate that an object can be found in nature ([158] of the spec.). Thus, the phrase "non-naturally-occurring amino acids sequences" can be broadly interpreted to mean any amino acid sequences that do not occur in nature, or it can be narrowly interpreted to mean that the monomers have amino acid sequences that are not wild-type sequences (e.g. wild-type human LDL receptor A domain). However, Claim 93 also recites the limitation that the "non-naturally occurring LDL-receptor class A monomer domain variants comprise" the amino acid sequence recited in SEQ ID NO. 331. The amino acid sequence of

SEQ ID NO. 331 encompasses at least the wild-type human LDL receptor A domain (the "naturally occurring amino acid sequences"). Thus, the limitation provided by the SEQ ID NO 331 is in direct conflict with the limitation provided by the phrase "non-naturally occurring", which creates confusion about the metes and bounds of the instant invention. A person of ordinary skill in the art would not be able to define the structural limitation of the claimed polypeptide (i.e. amino acid sequence) of the claimed invention.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(Note: the instant claim numbers are in bold font.)

9. Claims 95, 100, 103, 106 and 107 are rejected under 35 U.S.C. 102(b) as being anticipated by Esser et al (Journal of Biological Chemistry. Vol. 263: 13282-13290; 1988). This rejection is necessitated by applicants' amendments to the claims.

The instant claims recite "a method for producing a polypeptide, said method comprising, expressing a nucleic acid encoding a polypeptide, thereby recombinantly expressing the polypeptide; wherein the polypeptide comprises a first LDL-receptor class A monomer domain variant and a second LDL-receptor class A monomer domain variant, wherein each of the first

and second LDL-receptor class A monomer domain variants have non-naturally-occurring amino acids sequences, wherein the first and second LDL-receptor class A monomer domain variants each have a binding specificity for a target molecule, wherein the two domain variants are linked by a heterologous linker, and wherein each of first and second the LDL-receptor class A monomer domain variants comprise the following sequence:

C-$X_{(3-15)}$-**C**-$X_{(4-15)}$-**C**-$X_{(6-7)}$-**C**-[N,D]-$X_{(3)}$-[D,E,N,Q,H,S,T]-**C**-$X_{(4-6)}$-D-E-$X_{(2-8)}$-**C** (SEQ ID NO:331)".

Esser et al, throughout the publication, teach generation and analysis of mutant ligand binding domains (reading on LDL receptor class A monomer domains) of the human LDL lipoprotein receptor (Abstract).

The reference teaches recombinantly making the LDL receptor polypeptides using polynucleotides (plasmids) that encode for the said polypeptides and transformation in E. coli cells (p. 13283, right col.), which reads on the expression method of **clms 95**.

The reference teaches the consensus sequences and mutations of the cysteine-rich repeat regions of the ligand binding domain based on human wild-type sequence (see pg 13284, Figure 1), which reads on a polypeptide comprising two "non-naturally" occurring LDL receptor class A monomer domains comprising six cysteines, as recited in **clm 95**, and the human monomer domain of **clm 106**. Each of the repeats listed in top panel of Figure 1 matches the consensus sequence of the instant **clm 95**. For example, the second repeat has 6 amino acid residues in between the first two C residues (which falls within the 3 to 15 range in the consensus); the repeat has 6 residues in between the 2nd and 3rd C residues (which falls within the 4 to 15 range

in the consensus); the repeat has 6 residues in between 3rd and 4th C residues (which falls within the 6 to 7 range); the repeat has a D residue after the 4th C residue, followed by 3 residues, and another D residue (which matches the consensus sequence requirement); the repeat has 4 residues after the 5th C residue, followed by a D, an E, and another two residues (which falls within the requirement of the consensus sequence). Thus, the repeats within the LDL receptor protein as indicated in the top panel of Figure 1 of the reference reads on the polypeptide comprising two A monomer domain variants of **clm 95**.

The reference also teaches linkers in between the repeats (or monomers) as indicated in Figures 1 and 2, which read on the 1-20 amino acids heterologous linker of **clms 95** and **107**.

The reference also teaches that the LDL receptor binds to various ligands (such as ApoB-100 of LDL and ApoE) through the cysteine-rich repeat regions (corresponding to the LDL receptor class A monomer domains), which reads on the monomer domains have a binding specificity for a target molecule of **clm 95.**

The reference teaches the polypeptides comprising the monomer domains are expressed in cells in the form of binding proteins (p. 13283-13284, bridging para.), which reads on the step of submitting the polypeptide to conditions that refold the polypeptide of **clm 100** because the polypeptides taught by the reference are properly folded into binding proteins.

The reference teaches the different polypeptides have different binding specificity to different ligands (see Abstract, Tables I and II, and pg13287+ of the reference), which reads on the limitations of **clm 103.**

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 95-98, 100, 101, 103, 106 and 107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Esser et al (Journal of Biological Chemistry. Vol. 263: 13282-13290; 1988), in view of Bajari et al (Biological Chemistry. Vol. 379: 1053-1062; Aug/Sept., 1998), and if necessary further in view of Russell et al (Journal of Biological Chemistry. Vol. 264 (36): 21682-21688; 1989), and Rudolph et al (The FASEB Journal. Vol. 10: p. 49-56; 1996).

Esser et al, throughout the publication, teach generation and analysis of mutant ligand binding domains (reading on LDL receptor class A monomer domains) of the human LDL lipoprotein receptor, as discussed above.

Esser et al do not specifically teach using bacteria phage display to express the LDL receptor A domain polypeptides as recited in **clms 96-98**. The reference also does not teach the method step of dialyzing the polypeptide as recited in **clm 101**.

However, Bajari et al, throughout the publication, teach using phage display to screen for LDL receptor A domain (LR8 fragments) or variants thereof that bind to a protein target (see

Abstract). The reference teaches expression of the polypeptides using phage display technology by employing MC1061 cells (*E. coli* cells) (p. 1059, para 1), which reads on the bacteriophage display recited in **clms 96-98**. The reference also teaches the standard protein purification step of dialysis after protein elution (p. 1060, 2nd para), which reads on the dialysis step of **clm 101**. The reference further teaches the advantage of using phage display, because it provides a powerful tool to manipulate (mutate) the LDL receptor A domains so that the receptor's ligand binding property can be altered for various purposes such as diagnostics or therapeutic interests (Abstract of the reference).

Russell et al, throughout the publication, teach mutational analysis of LDL receptor A domains (the monomer repeats) (see Abstract). The reference also teaches mutations of the LDL receptor A domains can lead to different ligand binding specificity and affinity (p. 21687, last para). The reference also teaches that the multiplicity of ligand binding repeats in the LDL receptor is necessary to all the receptor to bind to different ligands, and binding of each of the different ligands require interaction with different combinations of the repeats.

Rudolph et al, throughout the publication, teach in vitro folding of inclusion body proteins that are produced from recombinant protein expression (see Abstract). The reference teaches the need to dialyze the isolated proteins that are expressed recombinant, because the dialysis is usually required for proper refolding of isolated proteins (p. 51, right col., 2nd para).

A person of ordinary skill in the art would have been motivated at the time of the invention to use bacteriophage display system to express libraries of polypeptides that need to be screened, because bateriophage display system provides a powerful tool to manipulate (mutate) the LDL receptor monomer domains for various purposes, as discussed above. In addition,

Rudolph et al also teaches the need to mutate the different repeats (or monomers) of the LDL receptor domain for generation of LDL receptor with various binding specificity, as discussed above.

A person of ordinary skill in the art would have been motivated at the time of the invention to dialyze the isolated recombinant protein for subsequent assays, because Rudolph et al has demonstrated the need for dialysis step so that the isolated protein can be proper refolded, as discussed above.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since Bajari et al have demonstrated the success of expressing polypeptides with mutant LDL receptor repeats, and both Bajari and Rudolph et al have demonstrated the standard dialysis step in recombinant protein purification procedure is known and routine in the art.

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned

with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claim 95-98 and 103 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 21, 22, 24, 25, and 31 of copending Application No. 10/971,679 (20050164301; filed 10/22/04). Although the conflicting claims are not identical, they are not patentably distinct from each other because the '679 application claims a method of identifying a monomer domain (comprising 30+ amino acids) and multimers that bind to a target (Claims 21 and 24), for examples), and the monomers comprise the consensus sequence of the LDL receptor A domains (Claim 21).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached at 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Art Unit 1639
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JON EPPERSON, Ph.D.
PATENT EXAMINER